

Pandemic Plan for the Church

Ministering to the Community in a Time of Crisis

Pathophysiology of H5N1 Avian Influenza

The H5N1 strain of virus can trigger inflammatory proteins called *cytokines* to reach levels of more than ten times higher than in the common human flu virus H1N1. This inflammation can cause damage to a patient's lungs to the extent that they are unable to breathe.

HPAI H5N1

HPAI H5N1 is a subtype of influenza A virus that causes highly infectious, severe respiratory disease in birds. Because the H5N1 is so deadly to poultry, it is classified as highly pathogenic avian influenza (HPAI). "Highly pathogenic" refers to the virus's ability to produce serious illness. As a variant of avian influenza (bird flu), it is this highly pathogenic strain that has caused serious worldwide outbreaks in domestic poultry. As stated, the H5N1 was first discovered at Qinghai Lake in China, in 2005. It was at Qinghai Lake that the H5N1 spread to other migratory birds and has now been found in birds and other mammals across the world.

After first appearing in Asia, the HPAI H5N1 has spread globally. It has killed tens of millions of birds and causing the culling of hundreds of millions of others to prevent its spread. It has now jumped species and is able to infect over 200 types of mammals. It causes severe lung infection in mammals, and death is primarily due to viral pneumonia. Most references to "bird flu" in the popular media refer to this strain.

H5N1 Human Infection

Although this influenza A virus is considered an avian disease, it can cause illness in humans and many other animal species. It is one of the few avian influenza viruses to have crossed the species barrier to infect humans, and it is the deadliest of those that have crossed the barrier. Most cases in humans have resulted from contact with infected poultry or surfaces contaminated with secretions/excretions from infected birds, and other mammals.

Currently there is some evidence of limited human-to-human transmission of this virus. Research shows that when influenza viruses infect birds, the hemagglutinin surface protein of the virus is activated by acid in the entry pathway inside the host cell, enabling it to invade that cell. This acid is found in the gastrointestinal tract in birds. This is significant because the upper airways of the nasal cavities of mammals are more acidic than infected tissues of birds, enabling the avian virus to enter the cells of these tissues. Therefore, the H5N1 does not have the same effect on avian tissue as it does on mammalian tissue. What might infect but not kill ducks is

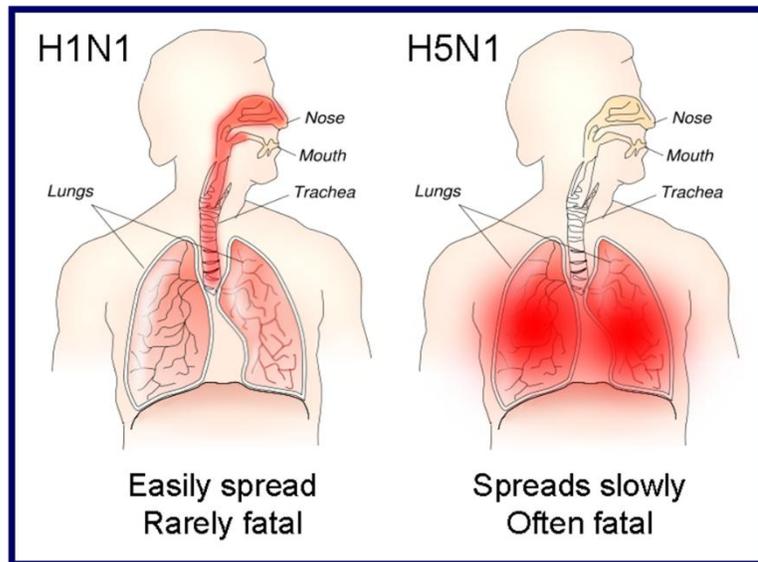
highly lethal to mammals. As researchers work with this strain, they have determined that it would take only one mutation to render the hemagglutinin protein more adaptable to acid and change this avian virus to a human virus.

Thus far H5N1 remains an avian virus that has not changed substantially since its emergence; human infections remain rare and sporadic. Most human cases of H5N1 virus infection are due to exposure through direct or indirect contact with household/backyard poultry or contaminated environments, as opposed to contact with commercial poultry or wild birds. However, the risk still remains of human infection where the virus is circulating in poultry and more recently dairy cows, and to people who are exposed to infected animals.

H5N1 and the Lower Respiratory Tract

The attachment of all influenza A virus strains to cells requires sialic acids. (For more information how this process takes place, please refer to the “Pathophysiology of Viral Diseases” in the “Influenza Viruses” section.) This refers to a group of acids that are attached to virtually all animal cells. Some are very tissue sensitive and can be found in only very specific cells. There are a number of chemically different forms of sialic acids, and influenza virus strains vary in their affinity to them. These differences may determine which animal species can be infected.

Avian influenza virus strains preferentially bind to sialic acids on epithelial cells lining the gastrointestinal tract of a duck. Human influenza virus, however, prefer the sialic acids on human respiratory epithelial cells found in the lower respiratory tract. Research has proven that the H5N1 avian virus prefers this type of sialic acid. This explains why it causes acute lower respiratory tract disease in humans and severe viral pneumonia.



H1N1 versus H5N1 pathologyⁱ

Due to the fact that these viruses are not present in the upper respiratory airway, it is not readily spread with sneezes. This also provides a rational explanation for why H5N1 viruses, at present, rarely infect and spread between humans – although they can replicate efficiently in the lungs.

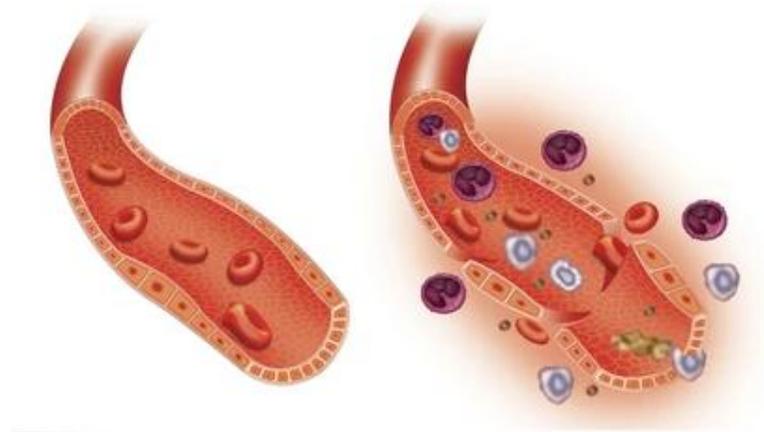
Pathophysiology of H5N1 Influenza

Pathophysiology of a disease describes the mechanisms by which it develops, progresses, and either persists or is resolved in its host. Although the lifecycle of the virus was discussed in the sections “Influenza Viruses,” and “Avian Influenza,” showing how the virus’ efforts in replication cause

The results of a study done by scientists in Hong Kong were published and made accessible online in 2005. The conclusion showed that the H5N1 strain of virus can trigger inflammatory proteins called *cytokines* to reach levels of more than ten times higher than in the common human flu virus H1N1. This inflammation can cause damage to a patient’s lungs to the extent that they are unable to breathe.

Inflammation

Inflammation is a normal response to injury or stress, bringing large amounts of white blood cells to the injured or infected area to aid in the healing process. Blood vessels in the affected tissue dilate (opening and widening of a normally narrow hollow part such as a blood vessel) and become more permeable (becoming easier for substances to pass through), allowing fluids, white blood cells, and other healing molecules to enter the damaged tissue. The area may become red, swollen, warm, and painful to touch. However, the dilated blood vessels provide the tissue with more oxygen and nutrients which aid in healing.



Arterial Inflammation with Componentsⁱⁱ

The white blood cells release chemicals that increase the blood flow to the area. As a result of the blood vessel dilation and the increase of blood flow and volume, the area may become red, with swelling and heat. This, in addition to the increase in permeability of the capillaries, and leakage of protein-rich fluid into tissue spaces, causing swelling of the tissue (edema). The heat comes from the additional blood coming to the area. An example of this is the swelling of a joint after an injury.

White blood cells accumulate at the sites of injury and inflammation. Some of these white blood cells help control pathogens (a microorganism that can cause disease). In bacterial infections, the resulting mass of white blood cells, bacterial cells, and damaged tissue may form a thick fluid called pus. When this accumulation of fluid and pus takes place in the alveoli of the lungs, gas exchange is greatly inhibited.

A normal inflammatory response should last as long as the infection or injury exists. Once an infection is controlled, phagocytes (cells that protect the body by ingesting harmful foreign particles) remove dead cells and other debris from the site.

Human Immune System

In order to explain the effect of these cytokines, and their role in inflammation, we must first discuss the human immune system. The immune system consists of specialized cells and organs and is the body's way of protecting itself from outside biological effects. It is divided into two sections: *innate immunity* and *adaptive immunity*.

The innate immune defense is general and nonspecific. It is present from birth and does not require prior exposure to pathogens to function. It protects against many types of pathogens (microorganisms that can cause disease) and functions the same way regardless of the type or the number of times the same pathogen invades.

When the innate immune system identifies a potentially harmful bacterium, virus, or other external invader, it unleashes white blood cells to surround and attack the foreign agent. This can cause swelling, redness, heat and pain in the body's tissues, otherwise known as inflammation, that in a healthy body eventually goes away. Some people, however, get stuck in the inflammation phase. This causes what is known as chronic inflammation.

The adaptive immune response, on the other hand, is very precise in targeting certain pathogens. These responses are carried out by specialized white blood cells called lymphocytes consisting of both T cells and B cells. These cells recognize foreign molecules by their antigens (a specific molecule or part of a molecule that the immune system recognizes as foreign) and react against them. T cells attach to foreign cells with unfamiliar antigens, such as the hemagglutinins and neuraminidases found on influenza viruses. The T cells interact directly with the antigens and destroy them. B cells respond indirectly by producing antibodies. An *antibody* is a protein produced in response to a specific antigen that combines with that antigen to neutralize, inhibit or destroy it.

Cytokine Storm

During the immune response to these antigens, macrophages, one of the most important cells in the immune system, gather at the site. It is these white blood cells that eliminate pathogens, present T cells to antigens, maintain homeostasis (modulate immune response in tissues), and produce cytokines. Cytokines are protein hormone like substances that act as messenger molecules and regulators in the immune system. They bind to specific cytokine receptors on other cells of the immune system and influence their activity.

Cytokines influence has varied cellular effects. They can act as synergists by enhancing the response to antigens and trigger inflammation. They can also act as antagonists by inhibiting signals and causing an anti-inflammatory response.

They play a role in immunity, hematopoiesis (formation of blood cells in bone marrow) and inflammation. In addition to carrying messages, they also behave as hormones and can produce effects on other cells close by.

Cytokines that regulate innate immunity are produced primarily in response to pathogens (any agent that can cause disease). Most cytokines influence leukocytes and endothelial cells (the layer of epithelial cells that form the inner lining of blood vessels and heart chambers) in order to promote and control inflammation.

When there is an excessive number of cytokines it can cause too much fluid to build up, this is called a *cytokine storm*. The phrase “cytokine storm” is a descriptive term to encompass a variety of cascading events that can ultimately result in multi-organ failure and death. A cytokine storm is a life-threatening condition caused by a severe, uncontrolled immune system reaction. Instead of protecting the body, this exaggerated response causes the immune system to overreact and release excessive amounts of pro-inflammatory cytokines into the bloodstream, triggering widespread inflammation that can damage organs and lead to multi-organ failure. One severe complication caused by this storm is known as acute respiratory distress syndrome (ARDS).

A cytokine storm is not unique to avian influenza, SARS, MERS, COVID-19, and the seasonal flu have similar pathology. During COVID-19, studies have been documented on the role of these pro-inflammatory cytokines, and related complications. ⁱⁱⁱ Please see the section “How to prevent Acute Respiratory Distress Syndrome” for more information on how to manage and even prevent these from being released.

Avian Influenza and Cytokine Storms

Since respiratory epithelial cells (cells that line the cavities in the body) are the primary target cell for replication of influenza viruses, it is pertinent to investigate the stimulation of cytokine production of H5N1 viruses in these particular cells.

Although other illnesses may trigger a cytokine storm, the H5N1 virus is also able to destroy the immune process by its ability to disable the present immune system. It can even

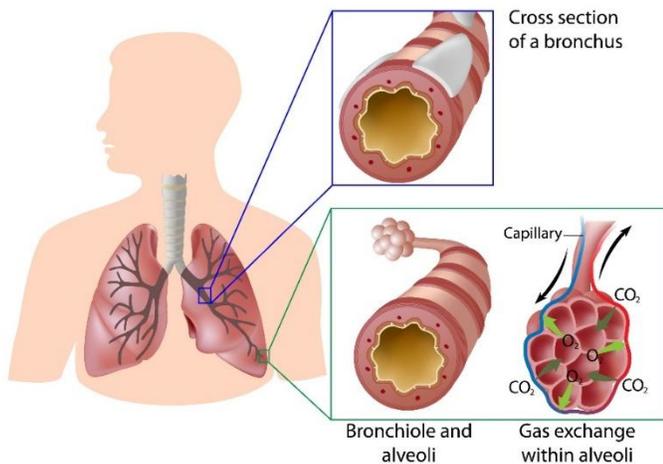
block the body's ability to build immunity against later infection by the same type of virus. During infection specific antibodies are produced to combat a virus; however, infection of the H5N1 shows an absence of these antibodies, this suggests they are destroyed during the infection process

Although cytokines help stimulate inflammation, they also contain regulatory components that inhibit over stimulation. The release of the inflammatory agent usually includes both inflammatory and anti-inflammatory signals. The H5N1 virus produces toxins that interfere with the control mechanisms of the immune system. The H5N1 is not only partially resistant to the cytokines that are involved in fighting viruses, but it also inhibits the production of anti-inflammatory cytokines. It causes a surge in the release of these inflammatory chemicals, and at the same time removes the control mechanisms to restrict their activity. In other words, it enhances the accelerator while impairing the brakes. The immune system basically goes out of control with no means of restraining it.

When the H5N1 virus comes in contact with the cells of the trachea and alveoli in the lungs, it stimulates the production of cytokines. The cytokines then stimulate inflammation with increased fluids. This increase of fluids results in damaging the alveoli and lung tissue. The fluid buildup in the lungs known as pulmonary edema leads to difficulty breathing and ARDS. The end stage result from a cytokine storm is sepsis and multiple organ dysfunction syndrome (MODS).

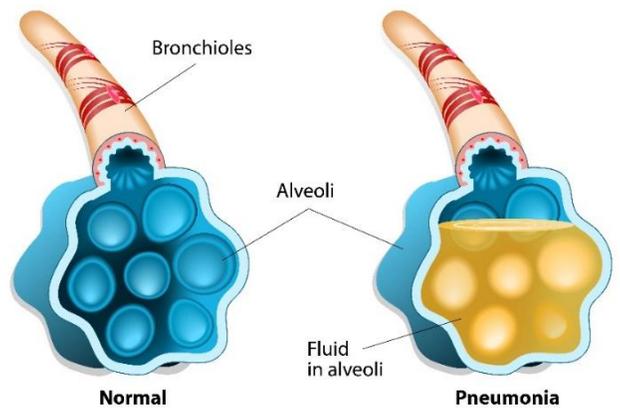
Alveoli and Gas Exchange Fluid in Alveoli

Human Lung Anatomy and Function



Alila Medical Media/Shutterstock.com^{iv}

PNEUMONIA

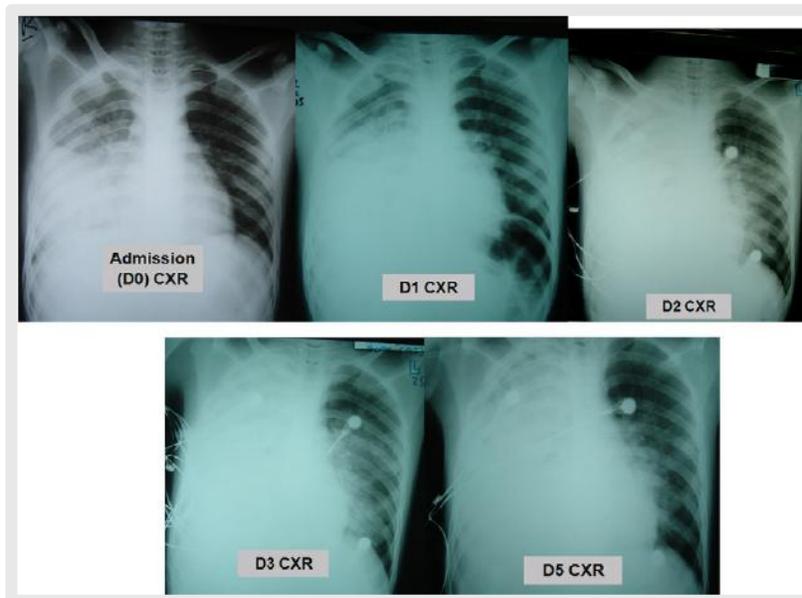


Designua/Shutterstock.com^v

The increase of cytokine production, as well as it causing the immune system to inhibit its release is what sets an H5N1 infection apart from other diseases. The hyper production of cytokines is very significant; and points out the way people experience this illness. The final result of a cytokine storm is:

- Sepsis
- Hypotension
- Tachycardia
- Acute respiratory distress syndrome (ARDS)
- Ischemia
- Uncontrollable hemorrhage
- Multi organ dysfunction syndrome (MODS)
- Multisystem organ failure

In addition to the H5N1, scientists believe this explains how the 1918 Influenza was so deadly, as well as the high death rate of the SARS outbreak in 2003. The excessive production of cytokines is what leads to the death of those infected with the avian flu virus, by stimulating excessive inflammation thus causing the airways to become blocked.



Chest X-ray series adult male with fatal H5N1^{vi}

Signs and Symptoms of H5N1 Influenza

The pathogenic course of this virus has been documented by doctors treating patients in the last 20 years. The virus replicates profusely within the first 24 hours causing severe damage

to respiratory tissues, sending the patient's immune response into lethal overdrive. Breathing difficulties develop about five days after the first symptoms leading to respiratory distress. A crackling sound develops upon inhalation, which is the air moving through the fluid building up in the alveoli. Almost all victims develop pneumonia. There is rapid deterioration, including multi-organ dysfunction and respiratory failure all within 3-5 days after symptom onset.

An average timeline for how the avian virus affects respiratory tissue in the following:

Day 1

- Severe bronchiolar and alveolar damage

Day 3-5

- Respiratory distress/failure

Day 7

- Hardly any viable lung tissue left to infect
- Still very strong viral replication

In a large number of patients, the H5N1 virus usually develops aggressively. The incubation period of two to eight days is longer than that of human seasonal flu which is two to three days. In some cases, the incubation period may take as long as 17 days. Incubation period is the amount of time between exposure to the disease and the development of signs and symptoms. For field investigations and monitoring of patient contacts, WHO (World Health Organization) recommends health care professionals use an incubation period of seven days.

Humans with avian flu may have the following signs and symptoms (many are similar to the seasonal human flu):

- Conjunctivitis
- Fever (over 100.4° degrees F)
- Cough
- Sore throat
- Headache
- Aching bones, joints and muscles
- Nasal congestion, and runny nose
- Bleeding from the nose
- Bleeding from the gums
- Malaise
- Loss of appetite/Nausea
- Abdominal pain
- Diarrhea

- Vomiting
- Neurological changes
- Altered level of consciousness/Seizures
- Chest pain
- Cold sweats and chills
- Headache
- Sleeping difficulties
- Lower respiratory tract infection, which includes breathing difficulties
- Sputum is sometimes bloody
- Chest pain
- Tachycardia
- Myocardial infarction
- Hypotension
- Acute encephalitis
- Acute Respiratory Distress
 - Crackling sound on inhalation
- Respiratory failure
- Multi-organ dysfunction

Patients with avian influenza can deteriorate rapidly, resulting in pneumonia, multiple organ failure, and death. The known pathogenicity is only the tip of the iceberg. There are likely to be additional pathogenetic mechanisms.

Diagnosing H5N1 Influenza

Avian influenza A virus infection in humans cannot be diagnosed by clinical signs and symptoms alone; laboratory testing is required. Avian influenza A virus infection is usually diagnosed by collecting a swab from the nose or throat of the sick person during the first few days of illness. This specimen is sent to a specialized lab set up with high levels of protection. There are approximately 140 designated laboratories of the Laboratory Response Network located in all 50 states of the United States of America.

Testing should be done when a patient has severe respiratory illness and clinical or epidemiological risk. Healthcare providers should contact their local or state health department as soon as possible to report any suspected human case of influenza H5N1 in the United States. Positive tests for influenza A H5N1 in the United States should be confirmed by Health and

Human Services (HHS) and the Centers for Disease Control (CDC), which has been designated as a WHO H5 Reference laboratory.

Treatment Options of H5N1 Influenza

According to WHO antiviral medications, such as oseltamivir can suppress viral replication and improve outcomes for patients, especially survival prospects. Oseltamivir, sold under the brand name Tamiflu, should be administered within 48 hours after the onset of symptoms for best effect. However, as avian influenza mortality rates are high, doctors may consider prescribing Oseltamivir for patients who were diagnosed later. For those with severe symptoms, doctors may have to increase the recommended daily dose, as well as treatment duration. Physicians should bear in mind that drug absorption may be severely impaired in patients with severe gastrointestinal symptoms. Antiviral medications have no effect on a cytokine storm.

Patients diagnosed with avian flu or who are suspected of having avian flu will be told to either remain at home or will be hospitalized (in isolation from other patients). Complications such as bacterial pneumonia are common in patients infected with H5N1 virus. These patients should be prescribed antibiotics; some may need extra oxygen. For more information on caring for a patient with Avian Influenza, please see the sections “Caring for the Sick,” and “Preventing a Cytokine Storm (ARDS).”

Pathophysiology of the 1918 Influenza Virus

American scientists believe that the 1918 Pandemic was so deadly because it triggered a tremendous immune response in the human body. This immune system response, or cytokine storm, causes the body to destroy its own healthy cells as well as infected cells. Most patients succumbed to severe respiratory complications secondary to rapidly progressing pneumonia.

Records from the 1918 Influenza of healthcare providers and journals of family members paint a grim picture of the process through which a patient responded to the virus. Archives of notes written by doctors and medical students depicted miserable deaths.

Their notes described patients who became short of breath and who appeared blue from cyanosis (lack of oxygen). The patients would gasp for hours struggling for breath as their lungs filled with fluid from the inflammation caused by the cytokine storm. A blood-tinged froth would come from their nose and mouth. Some patients would hallucinate and presented with an altered level of consciousness as their system was starved for air.

“As their lungs filled ... the patients became short of breath and increasingly cyanotic. After gasping for several hours, they became delirious and incontinent, and many died struggling to clear their airways of a blood-tinged froth that sometimes gushed from their nose and mouth. It was a dreadful business.”

--Isaac Starr, 3rd year medical student,
University of Pennsylvania, 1918. (The Influenza)^{vii}

Patients who first presented with the disease complained of a headache, sore throat, body and muscle aches, and an unproductive cough. These symptoms are eerily similar to seasonal influenza. However, the most common sign of the 1918 Influenza was a fever that lasted for several days. Many bled through the nose due to irritated mucous membranes. Secondary infections of bacterial pneumonia and bronchitis also contributed to the cause of death.

Pathophysiology HPAI H5N1 Compared to the 1918 Influenza Virus

The 1918 Influenza virus was obtained from the lung tissue from the corpse of an Inuit woman who died from the disease in an Alaskan village. Her body was retrieved from her grave below the permafrost level by Dr. Johan Hultin in July 1997. The tissue samples were sent to Dr. Jeffery Taubenberger (Armed Forces Institute of Pathology, Acting Director of National Institute of Allergy and Infectious Diseases, National Institutes of Health) who spent ten years reconstructing the virus and sequencing the genome to determine how the virus penetrates and infects the human cell.

Some things that Dr. Taubenberger discovered were that the 1918 Influenza virus had a close resemblance to the H5N1 avian strain circulating today. The 1918 virus had both human and bird flu origins; however, it managed to adapt to humans without acquiring genes from the existing human flu viruses. Several of the same mutations that differentiated the 1918 virus from circulating avian viruses are found in the H5N1 virus today.

Three of eight genes closely resemble each other, and the differences are only a small number of amino acids. This was proof that the 1918 virus was not human adapted but was entirely avian-like virus. There are only ten amino acid changes in genes that distinguish the 1918 virus from current avian viruses. A number of the same changes have been found in the recent circulating HPAI H5N1 virus.^{viii}

Avian viruses that are adapted to birds preferentially bind to sialic acid receptors with a specific sugar. Human-adapted influenza viruses preferentially bind with another. The switch from the avian receptor requires only one amino acid change. There is a great likeness between the 1918 virus and the H5N1 avian virus.

“1918 virus is the most bird-like of all mammalian flu viruses.”

Jeffrey Taubenberger
Armed Forces Institute of Pathology^{ix}

Dr. Taubenberger’s experiments with mice compared the H5N1 and the 1918 Influenza viruses determining that the H5N1 has a more rapid onset, with an overwhelming induction of cytokines. There was also a longer sustained replication with wider distribution in the lungs. Mice died in as little as three days, eventually all dying. Each virus attacked respiratory cells called pneumocytes (specialized epithelial cells that line the alveoli, or tiny air sacs of the lungs.)

Type 1 pneumocytes are thin, flat cells that cover most of the alveolar surface, forming the barrier for crucial gas exchange between the air and blood. Type 2 pneumocytes are cuboidal cells that secrete pulmonary surfactant. The surfactant is a substance that prevents the collapse of alveoli by reducing surface tension, allowing them to expand and contract properly during breathing and keeps the lungs elastic. It is responsible for the pliability of the lung tissue, which makes breathing possible. Surfactant also contains proteins that have microbial properties, helping to protect the lungs from infection.

The 1918 virus showed preference for Type 1 pneumocytes, responsible for air exchange. However, the H5N1 infects Type 2 pneumocytes, causing the loss of surfactant, and the collapse of the alveoli, making breathing impossible. The lung tissue is unable to repair itself.

It was also observed that not only did the mice suffer severe lung disease, but also their immune systems responded ferociously to the infection. Most of the mice became seriously ill within twenty-four hours and died within five days. This experiment proved to researchers that the host's inflammatory response is highly activated by the virus, causing severe damage and consequentially killing the host. This response is what made the virus so lethal.

In late 2011, Ron Fouchier and his team at the Erasmus Medical Center in Rotterdam, Netherlands, genetically modified the H5N1 virus to become airborne between ferrets. Ferrets have similar pulmonary receptors to humans and are a good model for medical experiments. The results showed that the H5N1 virus could acquire the ability to spread between mammals without mixing with other viruses or intermediate hosts such as pigs and thus poses a risk of launching another pandemic.^x

HPAI H5N1 Today

Health officials state that people who have died from the H5N1 circulating today have died in a similar manner to those who died during the 1918 pandemic. The main difference between the 1918 influenza virus and the H5N1 virus is that the current one has not yet mutated to become human-to-human transmissible. The study of the 1918 influenza has given great insight into the pathophysiology (the progression of a disease in the human body) as well as the societal effects this current virus will have if it ever becomes a pandemic.

In comparison, seasonal influenza viruses primarily cause inflammation, congestion, and some death to epithelial cells (tissue that line the airways) of the larger airways, with less inflammation to the alveoli (small air sacs where gas is exchanged). However, the H5N1 virus causes inflammation and congestion of the larger airways (trachea, bronchi, and bronchioles) in addition to causing extensive inflammation and damage to the alveoli. Patients literally drown due to the overreaction of their own immune system.

The virulence, structure, and origin of the HPAI H5N1 are very similar to the influenza virus that caused the 1918 Influenza Pandemic. Due to these similarities, the pathophysiology (the origin and development of a disease) of the 1918 Influenza is used as a model for what to expect if the current H5N1 Influenza strain were to become human-to-human transmissible. It is

suspected that a similar pandemic will take place if the H5N1 strain mutates as the H1N1 strain did nearly one hundred years ago.

ⁱ “H1N1 versus H5N1 Pathology.png,” Tim Vickers, Wikimedia Commons, May 3, 2009, https://commons.wikimedia.org/wiki/File:H1N1_versus_H5N1_pathology.png, accessed September 10, 2025

ⁱⁱ “Illustration of an arterial inflammation with its components” Ilusmedical, Shutterstock, Stock Illustration ID: 72413827, March 3, 2011, <https://www.shutterstock.com/image-illustration/illustration-arterial-inflammation-components-72413827>, accessed September 11, 2025.

ⁱⁱⁱ “COVID-19 Infection: An Overview on Cytokine Storm and Related Interventions,” Montazersaheb, S., Hosseiniyan Khatibi, S.M., Hejazi, M.S. *et al. Virology Journal* 19, May 26, 2022 . <https://doi.org/10.1186/s12985-022-01814-1https://virologyj.biomedcentral.com/articles/10.1186/s12985-022-01814-1#citeas>, Accessed September 4, 2025

^{iv} Alila Medical Media/Shutterstock.com, <http://www.shutterstock.com/pic-96426923.html>

^v Designua/Shutterstock.com, <http://www.shutterstock.com/pic-214353118.html>

^{vi} “Avian Influenza – A Review for Doctors in Travel Medicine,” W.R.J. Talor, E. Burnhan, et.al., *Travel Medicine and Infectious Diseases*, “Science Direct,” Volume 8, Issue 1, January 2010, pp 1-12, <https://www.sciencedirect.com/science/article/pii/S1477893909001628>, accessed September 11, 2025

^{vii} “The Great Influenza, The Story of the Deadliest Pandemic in History,” John H. Barry, Penguin Books, 80 Strand, London, WC2R 0RL, England, 2004, p 227

^{viii} “Evidence of an Absence: The Genetic Origins of the 1918 Pandemic Influenza Virus,” Ann H. Reid, Jeffery K. Taubenberger, Thomas G. Fanning, National Library of Medicine, November 2004, <https://pmc.ncbi.nlm.nih.gov/articles/PMC7097663/>, accessed September 8, 2025

^{ix} “The 1918 Flu Virus Resurrected”, Jeffrey Taubenberger, Armed Forces Institute of Pathology, *Nature*, October 5, 2005; 437, National Library of Medicine, <https://pmc.ncbi.nlm.nih.gov/articles/PMC7095040/>, Accessed September 6, 2025

^x “Fouchier Study Reveals Changes Enabling Airborne Spread of H5N1,” Robert Roos, CIDRAP News, University of Minnesota, June 21, 2012, <https://www.cidrap.umn.edu/avian-influenza-bird-flu/fouchier-study-reveals-changes-enabling-airborne-spread-h5n1>, Accessed September 19, 2025